considered
/Kevin K. Hill/
September 21, 2010

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Sudhir Agrawal, Lakshmi Bhagat, Dong Yu and Ekambar R. Kandimalla		
Application No.:	10/757,345	Group:	1633
Filed:	January 14, 2004	Examiner:	Hill, Kevin Kai
Confirmation No.:	3490		
For:	MODULATION OF IMMUNOSTIMULATORY PROPERTIES OF OLIGONUCLEOTIDE-BASED COMPOUNDS BY UTILIZING MODIFIED IMMUNOSTIMULATORY DINUCLEOTIDES		

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CERTIFICATE OF MAILING

I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as First Class Mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 or is being facsimile transmitted to the United States Patent and Trademark Office on the date indicated below.

Date: September 17 2010

Signature: Joseph C Zucchero

Printed Name: Joseph C Zucchero

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DECLARATION PURSUANT TO 37 C.F.R. §1.132

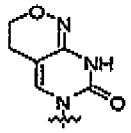
Dear Sirs:

I, Ekambar Kandimalla hereby declare as follows.

1. I am employed by Idera Pharmaceuticals, Inc. in the position of Vice President of Discovery. A copy of my *Curriculum vitae* is attached as Exhibit 1.

2. I understand that the Office Action mailed from the US PTO on April 16, 2010, interprets the terms "P-base" and "dP" to describe a genus and, absent to evidence to the contrary, the instantly claimed pyrrolo-[2,3-d]-pyrimidine nucleoside analog species, 2-oxo-7-deaza-8-methyl purine is an art recognized species thereof.

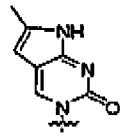
3. As shown in Exhibits 2-4, P-base or, alternatively, dP are common names used to identify a particular nucleotide having the structure:



P Base

Therefore, the terms P-base or dP do not represent a genus of nucleotides.

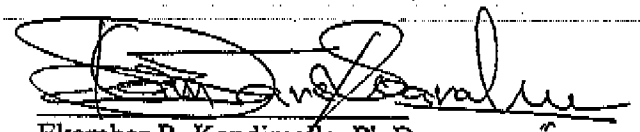
5. Furthermore, as shown in Exhibits 5-6, Pyrrolo-dC is the common name used to identify a distinct nucleotide having the structure:



Pyrrolo Base

6. Although Figure 4 of Woo et al. (Nucleic Acids Res. 24(13):2470-2475, 1996) depicts a nucleotide having the structure of pyrrolo-dC and labels this nucleotide as dP, as demonstrated by exhibits submitted herewith, the labeling of the pyrrolo-dC nucleotide as "dP" by Woo et al. was in error.

7. I hereby further declare that all statements made herein of my own knowledge are true and all statements made on information and belief are believed to be true and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Signed: 

Ekambar R. Kandimalla, Ph.D.

Dated: Sep. 17, 2010.

EKAMBAR R. KANDIMALLA
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Employment

01/2008 – Present	Vice President of Discovery, Idera Pharmaceuticals.
07/2003 – 12/2007	Senior Director of Research, Idera Pharmaceuticals (formerly Hybridon, Inc.). TLR targeted immunotherapeutics.
08/1999 – 06/2003	Director of Antisense and Functional Genomics, Hybridon, Inc. Application of antisense technology for functional genomics - Antisense oligonucleotide design, synthesis and target validation, fluorescence based PCR probes and primers, CpG-oligodeoxynucleotide-ased immunotherapeutics, preclinical studies of antisense oligos.
07/1993 - 07/1999	Sr. Research Scientist, Hybridon, Inc. Design, synthesis, biophysical and biochemical studies of modified antisense and triplex-forming oligos; Studies of the interaction of oligos with biological macromolecules; Solid phase attachment of oligos for diagnostic and analytical uses.
06/1992 - 06/1993	Research Scientist, Hybridon, Inc. Design, synthesis, biophysical and biochemical studies of modified antisense oligonucleotides
09/1987 - 06/1992	Research Associate, Department of Chemistry, University of Alberta. Molecular recognition of nucleic acids; Design, and synthesis of sequence specific minor groove binding peptide antibiotics as anticancer and gene expression control agents; Structural aspects of modified RNA and DNA oligonucleotides; Biophysical, biochemical and molecular biological studies on DNA-binding agents and proteins.
01/1985 - 09/1987	Research Associate, Molecular Biophysics Unit, Indian Institute of Science. Design, synthesis and nucleic acid binding studies of new analogs of DNA binding peptide antibiotics netropsin and distamycin.
02/1981 - 12/1984	Jr. and Sr. Research Fellow, School of Chemistry, Andhra University. Graduate student.

Education

Ph.D.	Chemistry, Andhra University, India	1984
M.Sc.	Biochemistry, Andhra University, India	1980
B.Sc.	Chemistry (Major) & Botony and Zoology, Andhra University, India	1978

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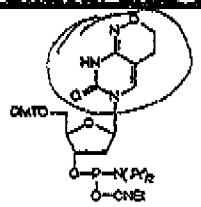
Issued/granted Patents

15. Short immunomodulatory oligonucleotides (US/7,354,907)
14. Modulation of immunostimulatory properties of oligonucleotide-based compounds by optimal presentation of 5' ends (US/7,276,489)
13. Modulation of immunostimulatory activity of immunostimulatory oligonucleotide analogs by positional chemical changes (US/7,262,286)
12. Modulation of oligonucleotide CpG-mediated immune stimulation by positional modification of nucleosides (US/7,176,296)
11. Modulation of oligonucleotide CpG-mediated immune stimulation by positional modification of nucleosides (US/7,115,579)
10. Modulation of oligonucleotide CpG-mediated immune stimulation by positional modification of nucleosides (US/7,105,495)
9. Pseudo-cyclic oligonucleobases (US/6,383,752)
8. Cooperative oligonucleotides (US/6,372,427).
7. Affinity-based purification of oligonucleotides using soluble multimeric oligonucleotides (US/5,912,332).
6. Mixed backbone antisense oligonucleotides conatining 2'-5'-ribonucleotide- and 3'-5'-deoxyribonucleotide segments (US/5,886,165).
5. Integrated oligonucleotides (US/5,739,308).
4. Triplex-forming antisense oligonucleotides having abasic linkers targeting nucleic acids comprising mixed sequences of purines and pyrimidines (US/5,693,773).
3. Pseudo-cyclic oligonucleobases (EP1086216B1)
2. Oligonucleotide alkylphosphonates and alkylphosphonothioates (EP0677056B1).
1. Foldback triplex-forming oligonucleotides (EP0680489B1)

Glen Research: P-base



Catalog Number: 10-1047-xx
Description: dP-CE Phosphoramidite

5H,8H-3,4-dihydro-pyrimido[4,5-c][1,2]oxazin-7-one,8-[(5'-dimethoxytrityl- -D-deoxyribofuranosyl),3'-[(2-cyanoethyl)-(N,N-diisopropyl)]-phosphoramidite

Formula: $C_{41}H_{50}N_5O_8P$ M.W.: 771.85 F.W.: 330.23

Diluent: Anhydrous Acetonitrile
Coupling: No changes needed from standard method recommended by synthesizer manufacturer.
Deprotection: No changes needed from standard method recommended by synthesizer manufacturer.
Storage: Refrigerated storage, maximum of 2-8°C, dry
Stability in Solution: 24 hours

Catalog Information | Material Safety Data Sheet

EXTINCTION DATA

Item	Nucleoside	Max-1	Emax-1	Max-2	Emax-2	E260
		(nm)	(ml/µmole)	nm	(ml/µmole)	(ml/µmole)
10-1047	dP	294	6.7	231	7.4	2.9

LITERATURE HIGHLIGHTS

Glen Report 9.1: PROPERTIES OF OLIGONUCLEOTIDES CONTAINING THE BASES P AND K
Glen Report 8.1: NEW UNIVERSAL AND DEGENERATE BASES

DILUTION/COUPLING DATA

The table below shows pack size data and, for solutions, dilutions and approximate couplings based on normal priming procedures. Please link for more detailed usage information with the various synthesizers.

ABI 392/394									
Cat.No.	Pack Size	Grams/ Pack	0.1M Dil. (mL)	LV40	LV200	40nm	0.2µm	1µm	10µm
				Approximate Number of Additions					
10-1047-02	0.25grams	.25grams	3.24	94.67	56.8	35.5	25.82	18.93	4.73
10-1047-90	100µmoles	.077grams	1	20	12	7.5	5.45	4	1

Expedite									
Cat.No.	Pack Size	Grams/ Pack	Dilution (mL)	Molarity	50nm	0.2µm	1µm	15µm	
				Approximate Number of Additions					
10-1047-02	0.25grams	.25grams	4.83	.067	90.2	56.38	41	5.64	
10-1047-90	100µmoles	.077grams	1.5	.067	23.6	14.75	10.73	1.48	

Beckman									
Cat.No.	Pack Size	Grams/ Pack	Dilution (mL)	Molarity	30nm	200nm	1000nm		
				Approximate Number of Additions					
10-1047-02	0.25grams	.25grams	4.83	.067	91.8	57.38	41.73		
10-1047-90	100µmoles	.077grams	1.5	.067	23.2	15.75	11.45		

05/03/2010 | http://www.glenres.com/ProductFiles/10-1047.html

Exhibit 2

Agrawal dP

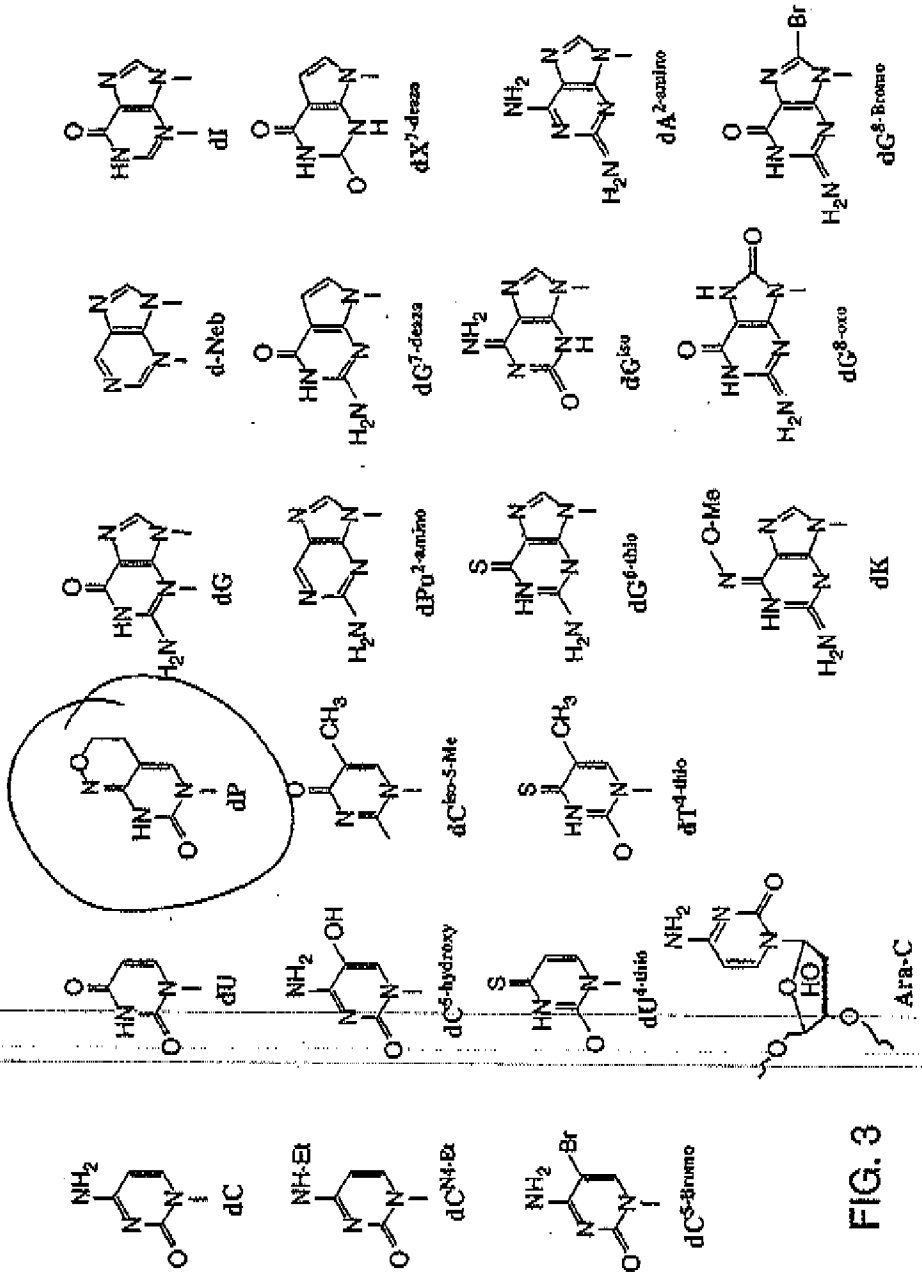


FIG. 3

Exhibit 3

Kandimalla 2001
Bioorg & Med Chem
p. 808 Fig. 2, panel 7
deoxy-P-base-nucleoside

resulted in a significant increase in immunostimulatory activity.[21] In addition, we have also shown that an accessible 5′-end, but not 3′-end, was critical for immunostimulatory activity of CpG-PS-oligos.[22]

The precise structural requirements and specific functional groups of the CpG-motif necessary for the recognition of protein/receptor factor that is responsible for immune stimulation have not yet been studied in detail. In this paper, we describe the results of a systematic study in which natural cytosine or guanine in a CpG-motif was replaced with a number of pyrimidine or purine analogues. The purpose of this study was to understand which functional groups of cytosine and guanine could be involved in the recognition of and interaction with factors responsible for immune stimulation. The in vitro and in vivo studies of CpG-PS-oligos containing modified purine bases (R) suggest that the alteration of functional groups at positions 1, 2, and 6 of guanine (see Fig. 1 for structure and numbering) significantly decreased immunostimulatory activity, while the deletion of nitrogen at the 7-position (N7) had an insignificant impact. Similarly, studies with CpG-PS-oligos containing modified pyrimidine bases (Y) suggested that the alteration of functional groups at positions 2, 3, and 4 of cytosine (see Fig. 1 for structure and numbering) significantly decreased immunostimulatory activity. Substitution of a hydrophobic methyl group at the 5-position decreased immunostimulatory activity and a hydrophilic hydroxy group at the same position did not suppress immunostimulatory activity. This is the first report of the use of chemically modified pyrimidine (Y) or purine (R) bases in place of natural cytosine or guanine, respectively, in a CpG-motif of oligos for immunomodulatory effects. In this paper, we describe the structure–immunostimulatory activity relationships of YpG- and CpR-motif-containing-PS-oligos compared with those of CpG-motif-containing-PS-oligos.

cytidine (3), deoxy-5-hydroxycytidine (4), deoxyuridine (5), deoxy-N4-ethylcytidine (6), and deoxy-P-base nucleoside (7) (Fig. 2). The modified purine nucleobases

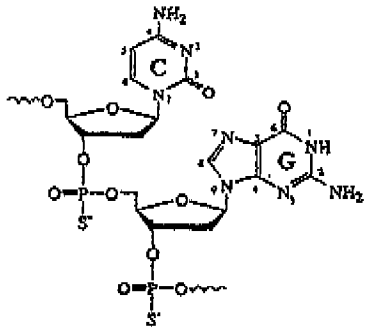


Figure 1. Chemical structure of a CpG-motif showing functional groups on cytosine and guanine that serve as hydrogen bond acceptor and donor groups.

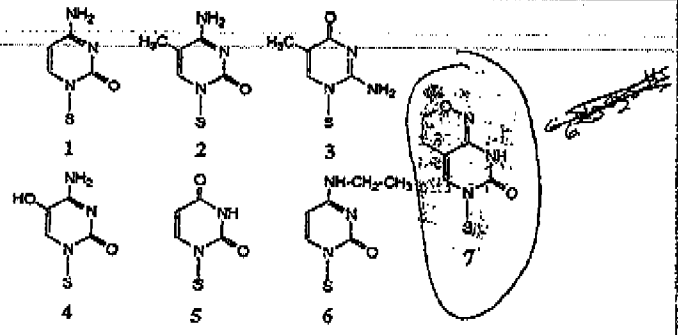
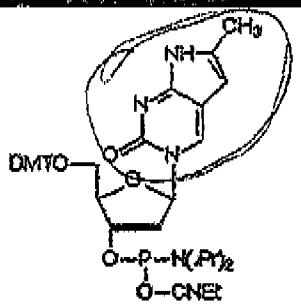


Figure 2. Chemical structures of cytosine (1) and its analogues (2–7) used in the study. S represents deoxyribose.

Exhibit 4

Glen Research: pyrrolo



Catalog Number: 10-1017-xx

Description: Pyrrolo-dC-CE Phosphorami

5'-Dimethoxytrityl-[6-methyl-pyrrolo-[2,3-d]-pyrimidine-2
2'-deoxyribonucleoside, 3'-[(2-cyanoethyl)-(N,N-diisopropyl)]-p

Formula: $C_{42}H_{50}N_5O_7P$ M.W.: 767.85

Diluent: Anhydrous Acetonitrile
Coupling: Standard coupling time. Use 0.02 M Iodine for Oxidation.
Deprotection: Ammonium Hydroxide for 24 hours at room temperature.
Storage: Refrigerated storage, maximum of 2-8°C, dry
Stability in Solution: 2-3 days
Please Note: Patents Pending.

Catalog Information	Material Safety Data Sheet

EXTINCTION DATA

Item	Nucleoside	Max-1	Emax-1	Max-2	Emax-2	E260
		(nm)	(ml/µmole)	nm	(ml/µmole)	(ml/µmole)
10-1017	Pyrrolo-dC	339	2.36	229	17.5	2.41

LITERATURE HIGHLIGHTS

Glen Report 15.1: Pyrrolo-C - a novel fluorescent nucleoside
Glen Report 16.1: Minor Base and Related Novel Phosphoramidites

DILUTION/COUPLING DATA

The table below shows pack size data and, for solutions, dilutions and approximate couplings based detailed usage information with the various synthesizers.

Exhibit 5

Liu JMB 2001
p. 466
pyrrolodC

While the smaller phage polymerase holds little or no structural homology with its prokaryotic and eukaryotic counterparts, if fundamental principles of nucleic acid topology and stability govern the design of an RNA polymerase, one might expect key features of the various elongation complexes to be similar (convergently evolved). In particular, von Hippel has proposed that heteroduplex energetics is a key component of the overall stability of an elongation complex (Wilson *et al.*, 1999). Thus, a minimal heteroduplex length (and therefore, bubble size) is proposed to be essential for a stable elongation complex. Here, we probe the size of the elongation bubble in the T7 enzyme.

Although complexes containing RNA shorter than about nine or ten nucleotides cannot be stably isolated, a recent study has shown that complexes paused at positions 10 to 14 nucleotides from the start site are much more stable (Mentesana *et al.*, 2000). A recent probing of similarly paused elongation complexes, using nucleases to estimate the footprint of the enzyme on the DNA and potassium permanganate to probe unpaired DNA bases within the bubble, provides evidence for a seven base-pair heteroduplex, with about a nine base open bubble (Huang & Sousa, 2000). The footprinting results in that study also illustrate clearly that probes which bind directly to the DNA to exert their effect, such as nucleases (and methy-

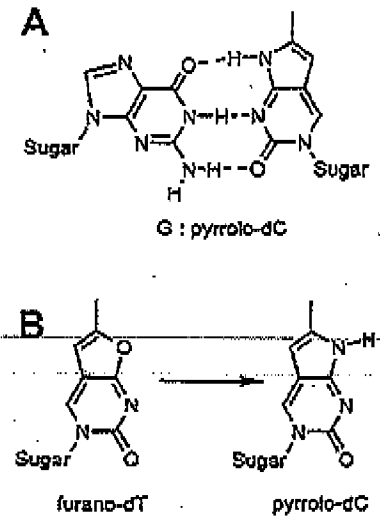


Figure 1. (a) During deprotection of a synthetic oligonucleotide, incorporated furano-dT (left) is quantitatively converted to pyrrolo-dC (right). (b) Structure of pyrrolo-dC (right) base-paired with guanine.

Exhibit 6